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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/33, 31/70, C07D 267/00, C07H 5/04, 5/06, 17/08

A1

(11) International Publication Number: **WO 99/00124**

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/US98/12174

(22) International Filing Date: 22 June 1998 (22.06.98)

(30) Priority Data:

60/050,810	26 June 1997 (26.06.97)	US
9812249.2	6 June 1998 (06.06.98)	GB

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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Published

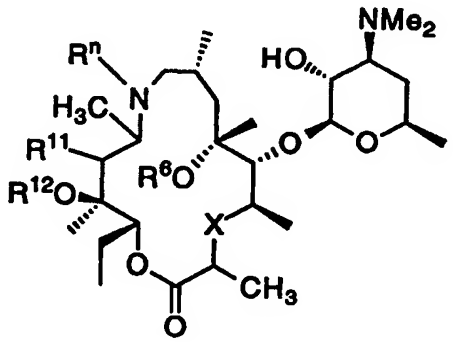
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 9A–AZALIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

(57) Abstract

Compounds are disclosed which are represented by formula (I); as well as salts and hydrates, thereof, wherein in part: X represents CH_2, CHF, CF_2, $C{=}CH_2$, CHSR, $CHCH_3$, C=S or CHOR. Pharmaceutical compositions and methods of treatment are also included.



(I)

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TITLE OF THE INVENTION

9A-AZALIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

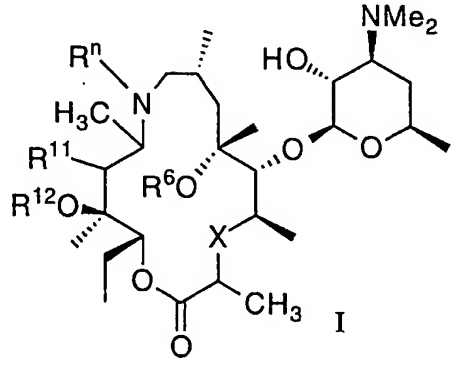
BACKGROUND OF THE INVENTION

The present invention relates to 9a-azalides, compositions containing such compounds and methods of use therefore. Azalides are structurally similar to erythromycin A, with the exception of the presence of a ring nitrogen atom at the 9a-position. The compounds of the invention are further distinguished from erythromycins and erythromycin-like compounds in that the cladinose moiety has been cleaved from the molecule.

The 9a-azalides of the present invention are potent antibiotics which are useful for the treatment of gram positive and gram negative organisms. As such the compounds find utility in human and veterinary medicine for the treatment of infections caused by susceptible organisms.

SUMMARY OF THE INVENTION

The present invention addresses a compound represented by formula I:

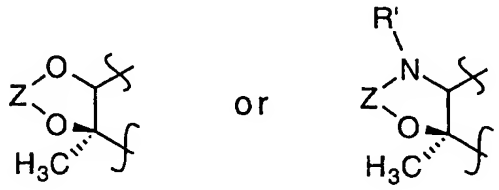


I

or a salt or hydrate thereof wherein:

R^{11} and R^{12} are taken separately or together;

when taken together, R^{11} and R^{12} taken with the intervening atoms form an additional ring as shown in the following structure:



wherein R' and Z are as defined below;

when taken separately, R^{11} is selected from the group consisting of: OH, OCH_3, NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$, and

R^{12} represents a member selected from the group consisting of: H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined below,

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

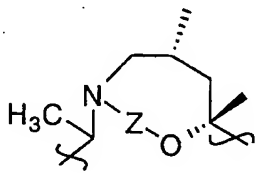
X represents CH_2, CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S or CHOR;

R represents H, CS_2CH_3, phenyl or C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

R^n represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above, and

R^6 represents H or CH_3,

or R^6 and R^n are taken in conjunction with the intervening atoms and form an additional ring as shown in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", $P(O)NR^nR"$, $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 in which X is as defined above;

R^z represents C_{1-6} alkyl or phenyl;

R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined, and

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined.

Also included is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included is a method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described in connection with the following definitions unless otherwise specified.

Alkyl refers to C1-6 straight or branched chain alkyl groups. The alkyl group can be uninterrupted or interrupted by 1-3

of O, $S(O)_y$ wherein y is 0, 1 or 2, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups. Included are moieties where the interrupting heteroatom is at either end of the alkyl group. Thus, a methylene spacer can be present which is adjacent to an interrupting moiety. Thus, this would include, for example, $-CH_2-O-$ and $-O-CH_2-$. When two or three of these interrupting groups is present, they may be separate or together. Me represents methyl.

Acyl refers to C_{1-5} alkyl-C(O)-.

When the group $-(CH_2)_nAr$ is present, the alkyl portion $-(CH_2)_n$ can be uninterrupted or interrupted as described above, with O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O). This includes groups where the interrupting atom is at either end of the chain. Thus, -C(O)-phenyl, -NH-phenyl, $-C(O)NH-(CH_2)_{1-10}$-phenyl, $-CH_2-O-$phenyl as well as like groups are included.

Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups selected from R^a. Examples of Ar include phenyl, naphthyl, quinolinyl, isoquinolinyl, pyridyl, imidazolyl, pyrrolyl, thiophenyl, benzothiazolyl, thiazolyl, furanyl, benzofuranyl, indolyl, fluorenonyl, dibenzofuranyl and naphthosultamyl.

Each R^a is independently selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a substituent groups are present, said substituents may be taken in combination with any intervening atoms to represent a 5-6 membered aromatic or non-aromatic ring, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, NH, NCH_3 or C(O) wherein y is as previously defined.

Halo means Cl, F, Br or I.

A preferred aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring represents CH_2, CHF or CF_2. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring

represents $C=CH_2$, C=S or CHSR. Within this subset of compounds, all other variables are as originally defined.

Yet another aspect of the invention relates to compounds of formula I wherein X contained in the azalide ring represents $CHCH_3$ or CHOR. Within this subset of compounds, all other variables are as originally defined.

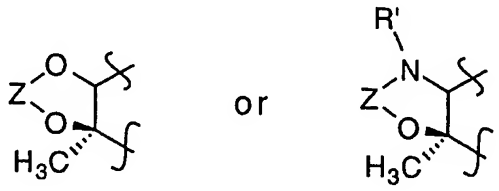
Another preferred aspect of the invention relates to compounds wherein R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$, and R^6 is H or CH_3. Within this subset of compounds all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined. Within this subset of compounds, all other variables are as originally defined.

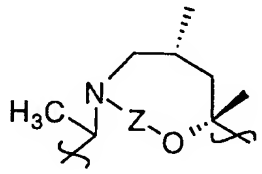
Another preferred aspect of the invention relates to compounds wherein R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:



in which Z is as originally described above. Within this subset all other variables are as originally defined.

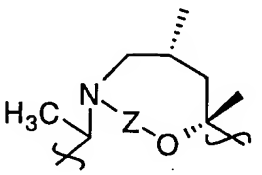
A preferred subset of compounds of the present invention relates to compounds of formula I wherein:

X represents CH_2, CHF or CF_2;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:

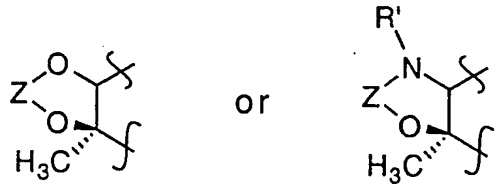


Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

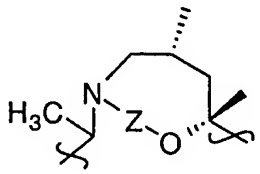
Another preferred subset of compounds of the invention relates to compounds of formula I wherein:

X represents $C=CH_2$, C=S or CHSR;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:

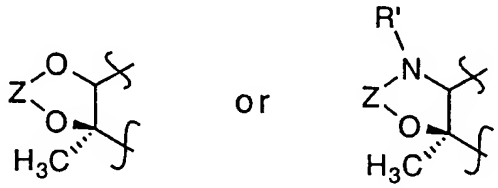


Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

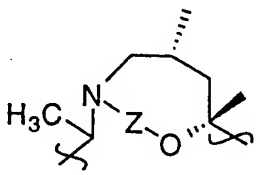
Yet another aspect of the invention relates to compounds of formula I wherein:

X represents $CHCH_3$ or CHOR;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:

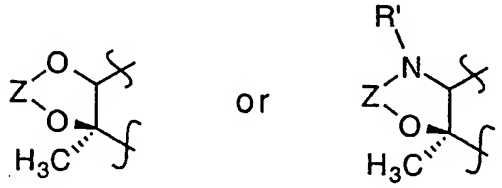


Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

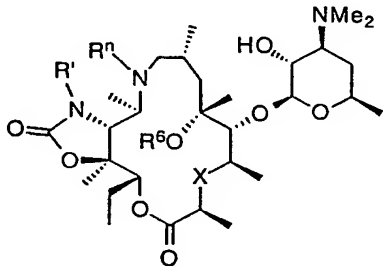
or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:

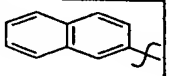
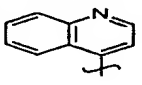


Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

Specific compounds which are included in the present invention are set forth below.

Table 1



#	X	R^n	R^6	R'	Ar
1	CH_2	CH_3	H	$(CH_2)_4Ar$	
2	CH_2	CH_3	H	$(CH_2)_4Ar$	
3	CH_2	CH_3	H	$(CH_2)_4Ar$	

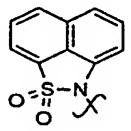
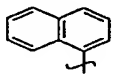
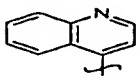
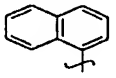
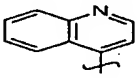
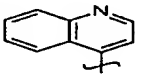
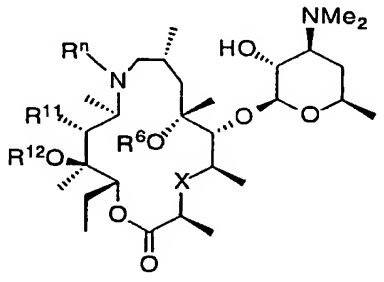
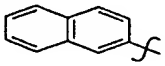
4	CH_2	CH_3	H	$(CH_2)_3Ar$	
5	CHF	CH_3	CH_3	$(CH_2)_4Ar$	
6	CF_2	CH_3	CH_3	$(CH_2)_4Ar$	
7	CH_2	---CH_2---		$(CH_2)_4Ar$	
8	CH_2	---CH_2---		$NH(CH_2)_3Ar$	
9	CH_2	CH_3	H	$NH(CH_2)_3Ar$	

Table 2



#	X	Rn	R6	R11	R12	Ar
10	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
11	CH_2	CH_3	H	OH	$(CH_2)_3Ar$	

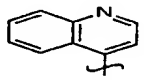
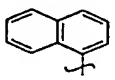
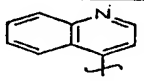
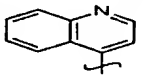
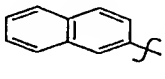
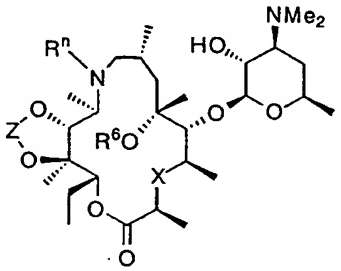
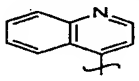
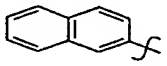
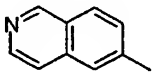
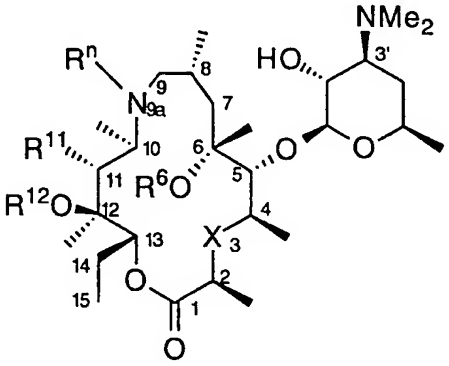
12	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
13	CHF	CH_3	CH_3	$O(CH_2)_4Ar$	H	
14	CH_2	CH_3	H	$S(CH_2)_4Ar$	H	
15	CH_2	$(CH_2)_4Ar$	H	OH	H	
16	CH_2	$(CH_2)_4SO_2Ar$	H	OH	H	
17	C=S	CH_3	CH_3	OH	H	------
18	CH_2	$-P(O)OCH_3-$		OH	H	------
19	C=S	$-P(O)OCH_3-$		OH	H	------
20	CH_2	$-COCH_2-$		OH	H	------
21	C=S	$-COCH_2-$		OH	H	------

Table 3



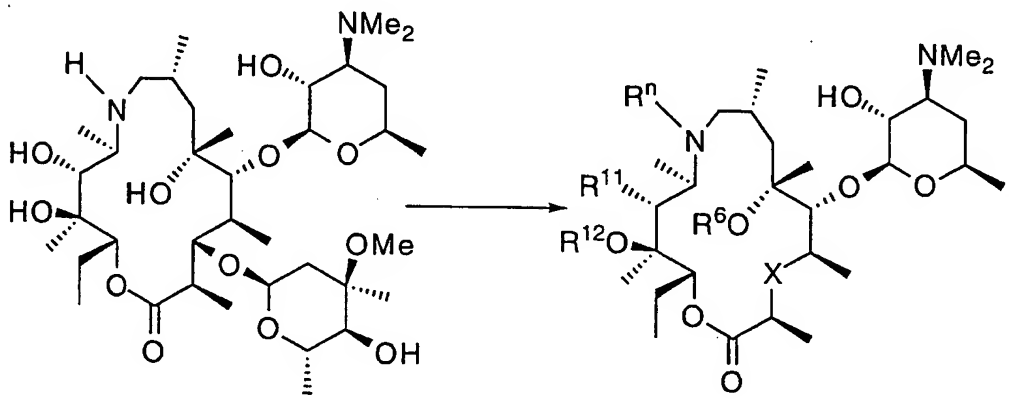
#	Z	X	Rn	R6	Ar
22	C=N(CH2)3Ar	CH2	CH3	H	
23	P(O)O(CH2)3Ar	CH2	CH3	H	
24	P(O)NH(CH2)3Ar	CH2	CH3	H	

Numbering of the 9a-azalides described herein is in accordance with the following scheme.



The compounds of the present invention are prepared from 9a-aza-9-deoxo-9a-homo-erythromycin A by a variety of synthetic routes. The process is illustrated by the following generic scheme:

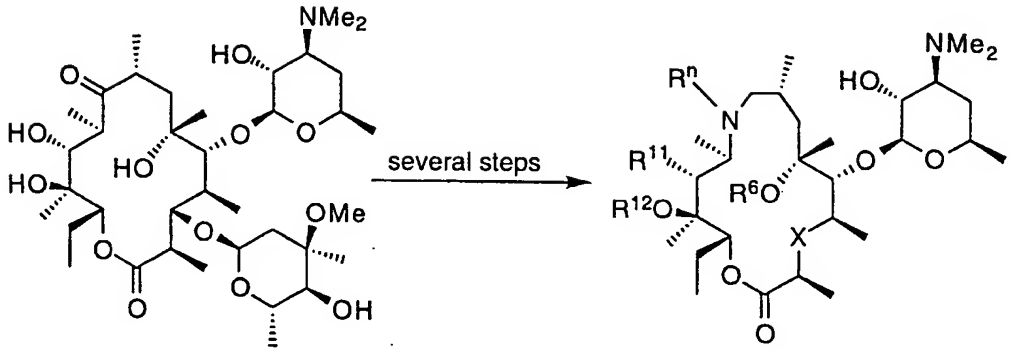
Scheme A



With reference to Scheme A, X, R^6, R^n, R^{11}, and R^{12}, are as defined with respect to the compounds of formula I.

Since 9a-aza-9-deoxo-9a-homo-erythromycin A is prepared from erythromycin, the compounds of the present invention are ultimately derived from erythromycin as shown in Scheme B. It will be further recognized that the the compounds of the present invention can be prepared from erythromycin without proceeding through the azalide intermediate shown above by simply altering the order of the steps described herein for the conversion of that intermediate to the compounds of the present invention and the steps required to introduce the 9a nitrogen.

Scheme B



At some point during the synthetic sequence, it is necessary to remove the cladinose attached at C-3 of the starting azalide. Depending on the exact nature of the final synthetic target, the cladinose removal may be best effected at either an early or late stage of the synthesis. This is generally accomplished by treating the macrolide with acid in either aqueous or alcoholic solution. Thus, a solution of the macrolide in an alcohol such as methanol, ethanol, or the like containing from 0.5 to 5% of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from 0°C to 30°C. Alternatively, a solution of the macrolide in a 0.1N to 1 N aqueous solution of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from about 0°C to 30°C. The reaction is worked up and the product macrolide isolated by first making the reaction mixture basic by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. If the reaction is run in an alcoholic solvent, the extraction procedure may be improved by first concentrating the reaction mixture under vacuum, preferably after addition of aqueous base to neutralize the acid. When working in the erythromycin series (ketone at C-9, free OH group at C-6), the C-9 ketone must be protected (e.g. as an oxime) before attempting to remove the cladinose under the acidic conditions described above. In the azalide series (C-9 ketone

removed with the addition of the 9a-nitrogen), no protection of a ketone at C-9 is necessary.

During alkylation of the C-3, 6, 11, or 12 hydroxyl group, it is necessary to protect the nitrogen at C-3' in order to prevent quaternization of the nitrogen. This can be accomplished by protection of the desosamine as the 2',3'-bis-CBZ derivative by using standard macrolide chemistry techniques. Alternatively, the 3'-nitrogen atom can be protected as an arylsulfonamide by N-demethylation followed by sulfonylation with an appropriate sulfonyl halide or sulfonic anhydride. It is not generally necessary to protect the 9a-nitrogen during alkylation reactions. However, protection of the 9a-nitrogen may be useful since it can alter the order of reactivity of the various hydroxyl groups to alkylation.

Some reactions, including but not limited to alkylation reactions, may also necessitate protection of other hydroxyl groups. This may be accomplished by protection as a silyl ether, an ester, a mixed carbonate, or any of a variety of hydroxyl protecting groups well-known to those skilled in the art.

Alkylation of the C-3, 6, 11, or 12 hydroxyl group may be accomplished by treating a solution of a suitably protected macrolide in a suitable solvent such as dimethylformamide, tetrahydrofuran, and the like with a strong base such as sodium hydride, potassium hexamethyl-disilazide, and the like at a temperature ranging from -40°C to 25°C for 1 to 30 minutes then adding a suitable alkylating reagent such as an alkyl iodide, an alkyl bromide, an alkyl trifluoromethanesulfonate, and epoxide, and the like and stirring the resulting reaction mixture at a temperature ranging from -40°C to 45°C for 15 minutes to 4 hours (appropriate temperature and length of time depends on the exact nature of the alkylating reagent).

Many of the compounds of the present invention contain fewer oxygen atoms attached to the macrolide ring than are present in erythromycin. Such deoxy analogs can be prepared by employing one of many deoxygenation methods for reductive removal of a hydroxyl group. For example, the hydroxyl group can be converted to a xanthate

ester by reaction with a base such as sodium hydride, potassium hexamethyldisilazide, and the like in a solution of a suitable solvent such as tetrahydrofuran, ether, dioxane and the like at temperatures ranging from -20°C to 30°C for 1 to 30 minutes followed by reaction of the resulting alkoxide with excess carbon disulfide and iodomethane to form a methyl xanthate. The methyl xanthate can be purified using standard techniques or, alternatively, may be subjected to the radical deoxygenation procedure without purification. A solution of the methyl xanthate in a suitable solvent such as toluene, benzene, and the like is treated with a radical initiator such as azobis-isobutyrylnitrile (AIBN), triethylborane, and the like and an excess of a hydride source such as tributyltin hydride, triphenyltin hydride, and the like at a temperature ranging from room temperature to 125°C for 1 to 24 hours. The reaction is worked up and the product macrolide isolated using standard macrolide chemistry techniques.

In compounds containing a cyclic carbamate moiety at C-11 and C-12 of the macrolide ring, the cyclic carbamate may be introduced into the erythromycin molecule before the ring expansion and incorporation of the 9a-nitrogen using standard techniques of macrolide chemistry which have been published in the literature and are well known to those skilled in the art. Once the cyclic carbamate moiety is in place, the 9a-nitrogen may be installed using the standard ring expansion techniques which have been previously published. For compounds containing an alkyl group appended to the nitrogen of the 11,12-cyclic carbamate, the alkyl group may either be incorporated during the construction of the cyclic carbamate or may be added to the completed cyclic carbamate via an alkylation procedure.

Alternatively, the 11,12-cyclic carbamate can be introduced at a stage in the sequence with the 9a nitrogen.

The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. The deprotected final product is then purified, as necessary, using standard techniques such as silica gel chromatography,

HPLC on silica gel or on reverse phase silica gel, and the like or by recrystallization.

The final product may be characterized structurally by standard techniques such as NMR, IR, MS and UV. For ease of handling, the final product, if not crystalline, may be lyophilized from, e.g., benzene, tert-butanol and the like, to afford an amorphous, easily handled solid.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The compounds of this invention may be used in a variety of pharmaceutical preparations. They may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize conventional formulating agents, and may include sustained release properties as well as rapid delivery forms. The preferred pharmaceutical composition is a table, capsule, suspension or solution, which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 25 mg to 1000 mg.

The preferred method of administration is oral.

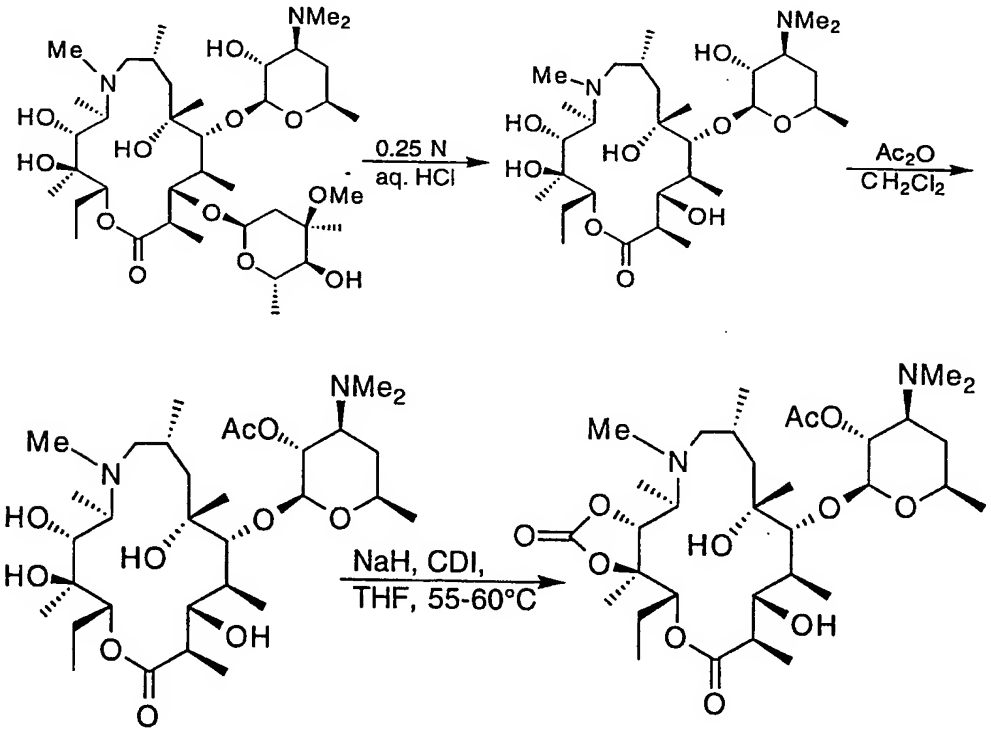
For adults, about 5-50 mg of the compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the compound given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended.

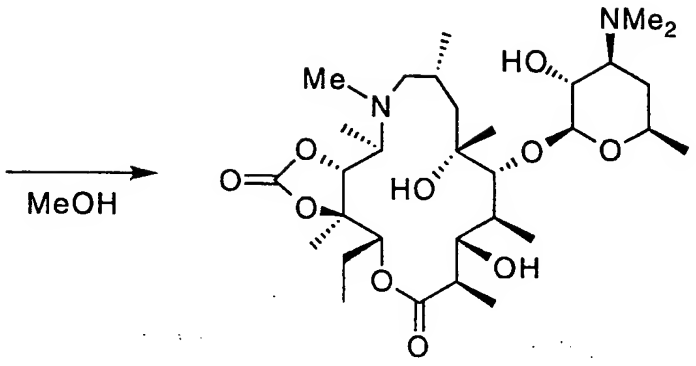
For severe infections caused by organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg may be recommended.

EXAMPLE 1

9-Deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A-11,12-carbonate





Step 1: 9-Deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A

A solution of 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A (2.0 g, 2.67 mmol) in 0.25N aqueous hydrochloric acid (100 mL) is stirred at room temperature for 24 hours. The solution is washed with chloroform (2 x 60 mL). The pH of the combined aqueous layers is adjusted to approximately 10 by dropwise addition of 5N aqueous sodium hydroxide and the aqueous layer is extracted with chloroform (3 x 60 mL). The combined organic extracts are dried over anhydrous potassium carbonate, filtered, and evaporated to give the title compound.

Step 2: 2'-O-Acetyl-9-deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A

A solution of 9-deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A (2.67 mmol) in dichloromethane (30 mL) stirred under a nitrogen atmosphere as acetic anhydride (0.54 mL, 5.7 mmol) is added. After stirring for 3 hours at room temperature, the solvent is removed *in vacuo*. The residual is dissolved in water (50 mL) and the pH adjusted to between 10-11 with 5N aqueous sodium hydroxide. The aqueous layer is extracted with dichloromethane (3 x 60 mL). The combined organic extracts are dried (anhydrous sodium sulfate), filtered, and evaporated to give the title compound .

Step 3: 2'-O-Acetyl-9-deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate

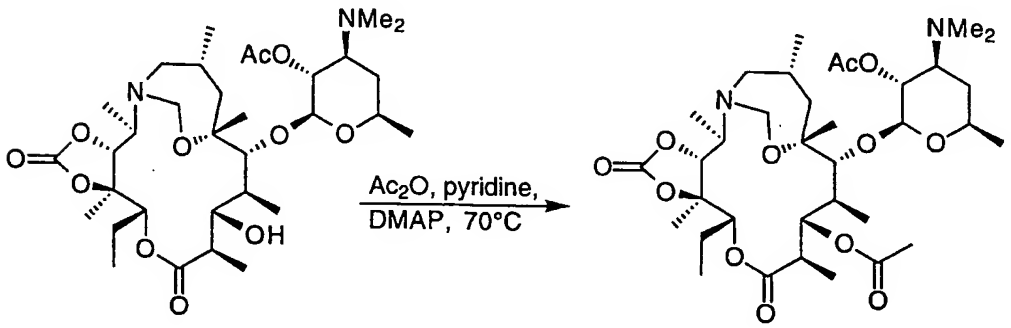
A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A (100 mg, 0.16 mmol) in anhydrous tetrahydrofuran (0.53 mL) is stirred at room temperature as sodium hydride (60% dispersion in mineral oil, 13.3 mg, 0.33 mmol) and 1,1'-carbonyldiimidazole (120.4 mg, 0.74 mmol) is added. The resulting mixture is stirred at 55-60°C. The reaction is partitioned between ethyl acetate and water. The aqueous layer is extracted twice with ethyl acetate. The combined organic layers are washed with brine, dried (anhydrous sodium sulfate), and evaporated. The crude product is purified on a silica gel column (12 g, 2.75 cm dia.) eluted with 1:1 hexane:acetone. The fractions containing product are combined and evaporated to give the title compound.

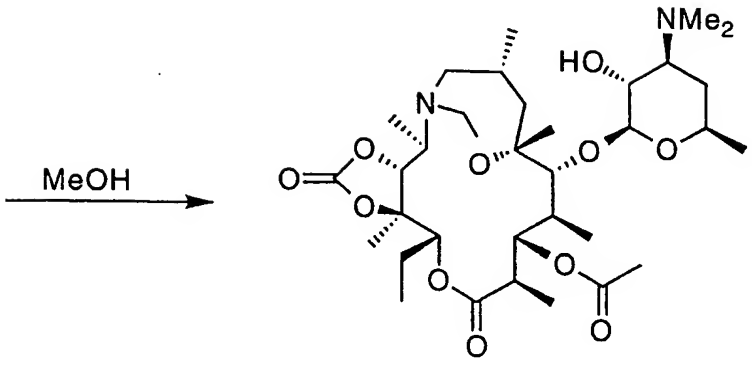
Step 4: 9-Deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate (15 mg, 0.023 mmol) in methanol (10 mL) is stirred overnight at room temperature then concentrated under vacuum. The product is dissolved in benzene (3 mL) and lyophilized to give the title compound.

EXAMPLE 2

3-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate





Step 1: 2',3-bis-(O-Acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate

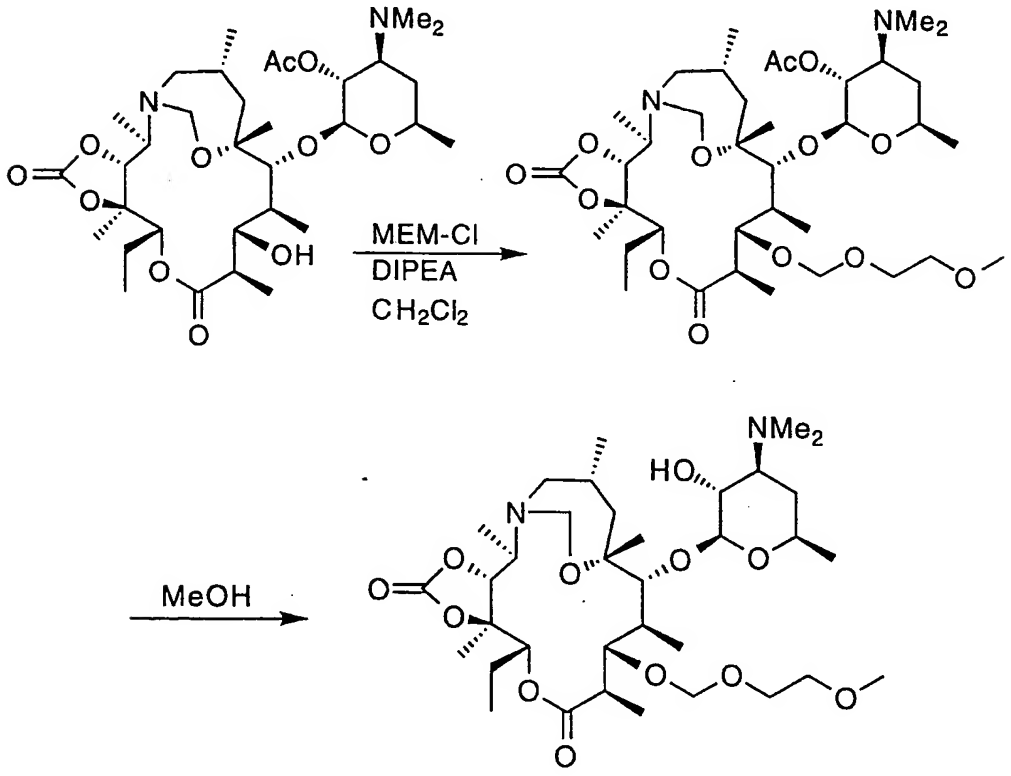
A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-11-O,12-O-carbonyl-9a-homoerythromycin A (32.8 mg, 0.05 mmol) in pyridine (1 mL) is stirred at room temperature as acetic anhydride (0.050 mL, 0.53 mmol) is added. The resulting solution is capped and stirred overnight. 4-Dimethylaminopyridine (3.8 mg, 0.031 mmol) and acetic anhydride (0.050 mL, 0.53 mmol) are added and the resulting solution is stirred at 70°C for 4 hours. The reaction mixture is then cooled to room temperature, concentrated and purified by column chromatography on silica gel (eluted with 1:1 hexane:acetone) to give the title compound.

Step 2: 3-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2',3-bis(O-acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate (28 mg, 0.039 mmol) in methanol (5 mL) is stirred for 24 h then concentrated under vacuum. The product is dissolved in benzene and lyophilized to give the title compound.

EXAMPLE 3

9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-9a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate (100 mg, 0.15 mmol) and N,N-diisopropylethylamine (0.133 mL, 0.76 mmol) in dichloromethane (0.5 mL) are stirred under a nitrogen atmosphere as 2-methoxyethoxymethyl chloride (0.087 mL, 0.76 mmol) is added dropwise. Additional N,N-diisopropylethylamine and 2-methoxyethoxymethyl chloride can be addedas necessary. After stirring, the reaction is partitioned between water and dichloromethane. The aqueous layer is extracted with dichloromethane and the combined

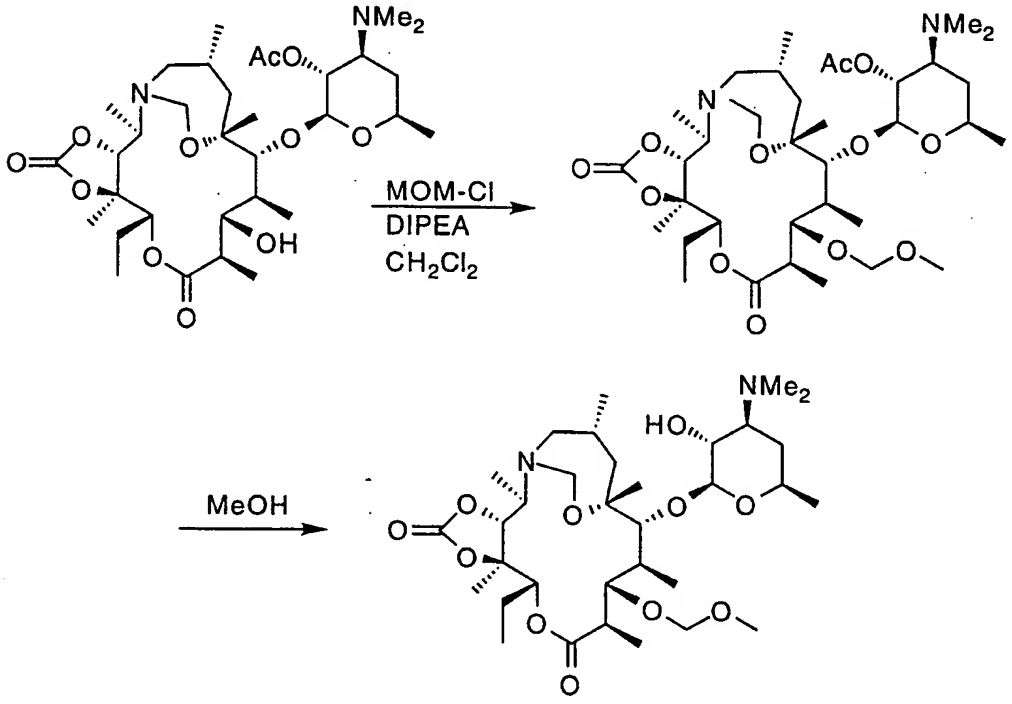
organic layers are dried over anhydrous sodium sulfate. Filtration and evaporation yield the crude material. The crude product (dissolved in 1:1 hexane:acetone) is loaded onto a silica gel column (30 g, 2.75 cm dia.) and eluted with 1:1 hexane:acetone. The appropriate fractions are combined, evaporated, and lyophilized from benzene to give the title compound.

Step 2: 9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-9a-homoerythromycin A 11,12-carbonate (27 mg, 0.036 mmol) is stirred in methanol overnight at room temperature. The reaction is concentrated lyophilized (from benzene) to give the title compound.

EXAMPLE 4

9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-9a-homoerythromycin A-11,12-carbonate



Step 1: 2'-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate (31.5 mg, 0.048 mmol) and N,N-diisopropylethylamine (0.046 mL, 0.264 mmol) in dichloromethane (1 mL) are stirred at room temperature as chloromethyl methyl ether (0.018 mL, 0.24 mmol) is added. Over 2.5 hours, N,N-diisopropylethylamine (0.046 mL, 0.046 mL, 0.092 mL, & 0.092 mL) and chloromethyl methyl ether (0.018 mL, 0.018 mL, 0.036 mL, & 0.036 mL) are added portionwise. The reaction is partitioned between saturated aqueous potassium carbonate and dichloromethane. The organic layer is dried (anhydrous potassium carbonate), filtered, and concentrated. The mixture is chromatographed

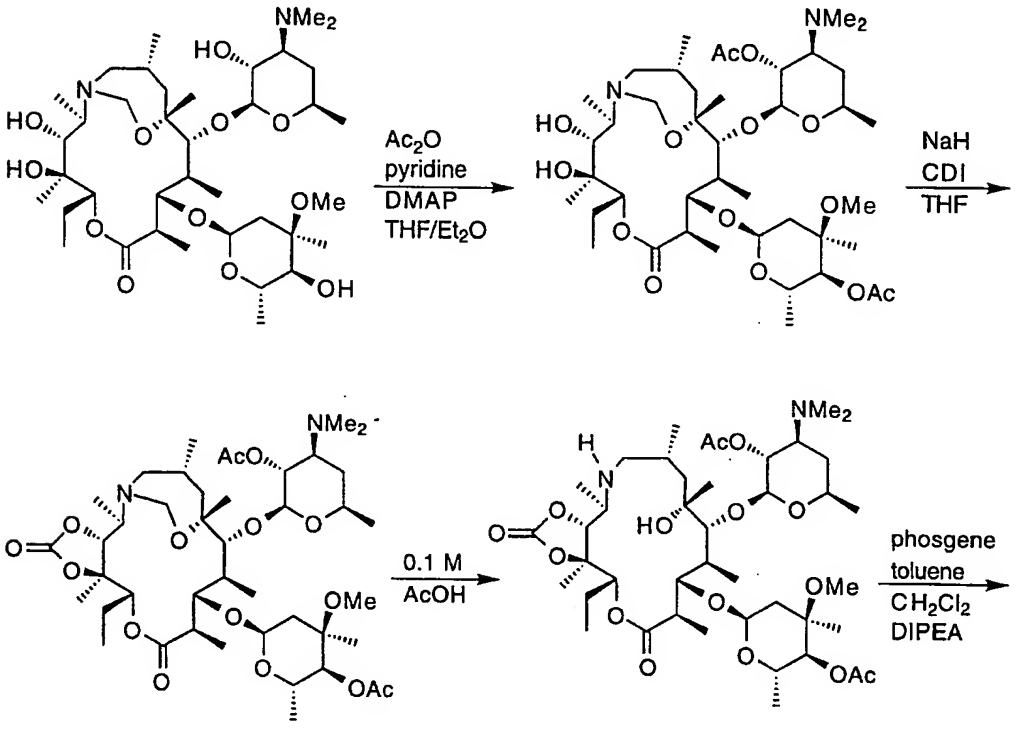
on a silica gel column (5g, 1.4 cm dia., 8 mL fractions) and the appropriate fraction is evaporated to give the title compound.

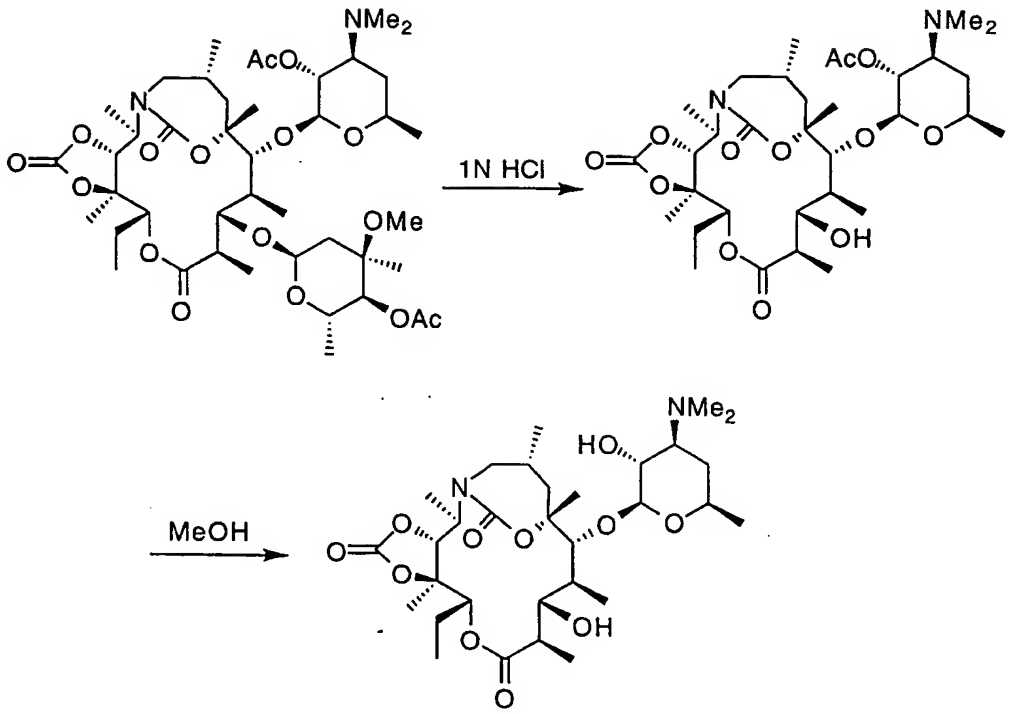
Step 2: 2'-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-9a-homoerythromycin A 11,12-carbonate (9.0 mg, 0.0126 mmol) in methanol (3 mL) is stirred, concentrated and the residue lyophilized from benzene to give the title compound.

EXAMPLE 5

9-Deoxo-9a-aza-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate





Step 1: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-N,6-O-methylene-9a-homoerythromycin A

A solution of 9-deoxo-9a-aza-9a,6-O-methylene-9a-homoerythromycin A (3.07 g, 4.1 mmol), 4-dimethylaminopyridine (125 mg, 1.02 mmol), and pyridine (3.5 mL, 43.3 mmol) in 5:1 ether:tetrahydrofuran (135 mL) is cooled to 0°C with stirring. Acetic anhydride (3.9 mL, 41.3 mmol) is added dropwise. The cooling bath is thereafter removed and the reaction allowed to stir at room temperature. The reaction is partitioned between ethyl acetate and saturated aqueous potassium carbonate. The organic layer is washed with brine, dried (anhydrous sodium sulfate), filtered, and evaporated to give the title compound.

Step 2: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-N,6-O-methylene-9a-homoerythromycin A 11,12-carbonate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a-N, 6-O-methylene-9a-homoerythromycin A (1.0 g, 1.2 mmol) in anhydrous

tetrahydrofuran (7 mL) is stirred at room temperature as sodium hydride (104 mg of 60% dispersion in mineral oil, 2.6 mmol) is added. 1,1'-Carbonyldiimidazole (0.88 g, 5.4 mmol) is then added with further stirring at 70°C. Saturated aqueous sodium bicarbonate is added dropwise. The aqueous layer is extracted twice with ethyl acetate. The combined organic layers are washed with 5% aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give the title compound.

Step 3: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 0.1 M aqueous acetic acid (250 mL) is added to 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-9a-homo-erythromycin A 11,12-carbonate (1.09 g, 1.2 mmol). The resulting suspension is stirred at room temperature for 8 hours. The aqueous layer is washed with ethyl acetate (5 mL). The aqueous layer is made basic by the dropwise addition of saturated aqueous potassium carbonate and extracted with ethyl acetate (2 x 250 mL). The combined organic layers are washed with brine, dried over anhydrous potassium carbonate, and evaporated to give the title compound.

Step 4: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (0.86 g, 1.02 mmol) and 4-dimethylaminopyridine (32.4 mg, 0.27 mmol) in dichloromethane (8 mL) is stirred under a nitrogen atmosphere. N,N-Diisopropylethylamine (8.0 mL, 45.9 mmol) is added followed by the dropwise addition of phosgene (20% in toluene, 8.0 mL, 20.3 mmol). The reaction is stirred at room temperature, and partitioned between dichloromethane and saturated aqueous potassium carbonate. The organic layer is washed with water, dried (anhydrous potassium carbonate), filtered, and evaporated to give the title compound.

Step 5: 2'-O-Acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate(1.29 g) in 0.86M aqueous hydrochloric acid (350 mL) is stirred at room temperature to completion. The solution is made basic with saturated aqueous potassium carbonate and extracted with ethyl acetate (3 x 300 mL). The combined organic layers are washed with brine, dried (anhydrous sodium sulfate), filtered, and evaporated to produce the crude product.

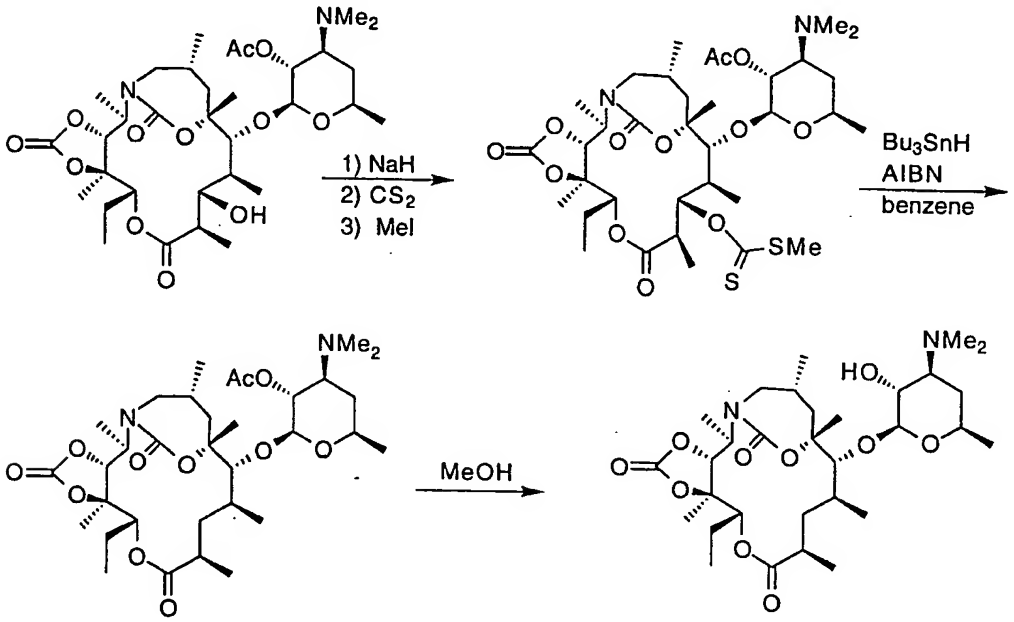
The crude solid is dissolved in 2:1 hexane:acetone and loaded onto a silica gel column (2.75 cm dia., 22 g of silica, 20 mL fractions), eluted with the same solvent system. The appropriate fractions can be combined, evaporated, and lyophilized (from benzene) to give the title compound.

Step 6: 3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-carbonyl-11-O,12-O-carbonyl-3-descladinosyl-9a-homoerythromycin A (11.1 mg, 0.017 mmol) is stirred in methanol (3 mL). The solvent is evaporated and the residue lyophilized (from benzene) to give the title compound.

EXAMPLE 6

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A-11,12-carbonate-9a-N,-6-O-carbamate



Step 1: 2'-O-Acetyl-3-descladinosyl-3-O-methylxanthyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate

A solution containing 2'-O-acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate (78.4 mg, 0.12 mmol) and N,N-dimethylformamide (2 mL) is cooled to -20°C and placed under a nitrogen atmosphere. After 15 minutes, the reaction is treated with carbon disulfide (0.011 mL, 0.18 mmol). After stirring for 2 minutes, iodomethane (0.011 mL, 0.18 mmol) is added. After 15 minutes, the resulting solution is allowed to warm to room temperature and stir for 3.33 hours. The reaction is partitioned between dichloromethane and saturated aqueous potassium carbonate. The aqueous layer is extracted twice with dichloromethane. The combined organic layers are washed with water (3x), dried over

anhydrous potassium carbonate, filtered, evaporated, and lyophilized (from benzene) to afford the title compound.

Step 2: 2'-O-Acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate

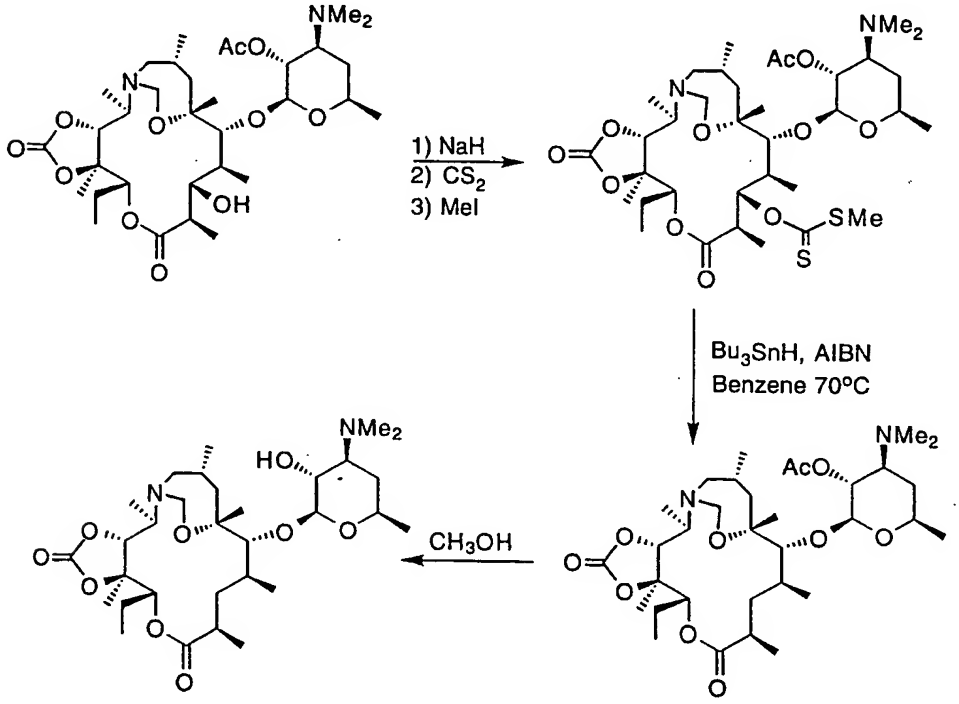
A solution of 2'-O-Acetyl-3-descladinosyl-3-O-xanthyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate (20.4 mg, 0.027 mmol) and 2,2'-azobisisobutyronitrile (1.0 mg, 0.006 mmol) in benzene (1.5 mL) is stirred under nitrogen as tributyltin hydride (0.022 mL, 0.082 mmol) is added. The resulting solution is stirred at 90°C for 2 hours. The solution is allowed to cool to room temperature, decanted (rinsing ppt. with benzene), and lyophilized to give the desired product.

Step 3: 3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate

A solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate in methanol (4 mL) is stirred overnight. The solvent is removed under vacuum, and the residue is lyophilized from benzene. The crude product is purified on a silica gel column (7 g, 0.75 inch diameter), eluted with 1:1 hexane:acetone. The appropriate fractions are combined, evaporated, and lyophilized from benzene to give the title compound.

EXAMPLE 7

3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-Acetyl-3-descladinosyl-3-O-methylxanthyl-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

Sodium hydride (166 mg of 60% oil dispersion, 4.14 mmol) is added to a cold (-20°C) solution of 2'-O-acetyl-3-descladinosyl-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (905 mg, 1.38 mmol) in anhydrous DMF (11 mL). The reaction mixture is stirred for 15 minutes at -20°C and carbon disulfide (0.124 mL, 2.09 mmol) is added. The mixture is stirred for 15 minutes at -20°C and iodomethane (0.129 mL, 2.09 mmol) is added. The bath is allowed to warm to -10°C, and the flask is removed and stirred at room temperature. The reaction mixture is poured into ethyl acetate. The organic layer is washed with

saturated aqueous $NaHCO_3$, dried over K_2CO_3, and filtered. Removal of solvent under reduced pressure affords the crude product.

Step 2: 2'-O-Acetyl-3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

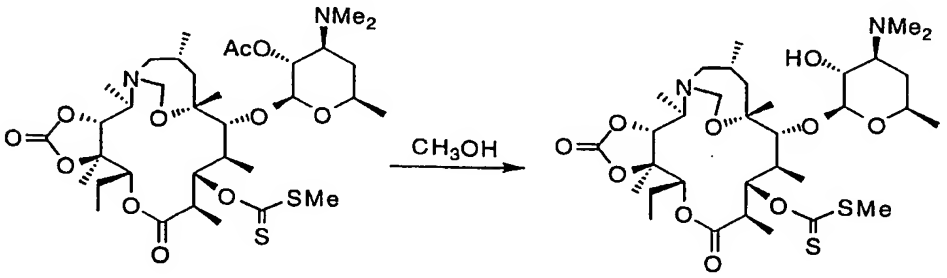
The product of step 1 and 23 mg of AIBN (0.14 eq) are dissolved in 20 mL benzene and stirred at 90°C. To this, 1.10 mL of Bu_3SnH is added and the reaction is heated at reflux for 4 hours. The reaction is cooled to room temperature and solvent removed under reduced pressure. The crude material is purified by silica chromatography eluting with 2:1 hexane:acetone. The fractions containing the desired material are combined and solvent removed under reduced pressure.

Step 3: 3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (537 mg) in methanol (30 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure to afford the crude product which can be purified by silica chromatography eluted with 1:1 hexane: acetone to afford the title compound.

EXAMPLE 8

3-descladinosyl-3-O-methylxanthyl-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

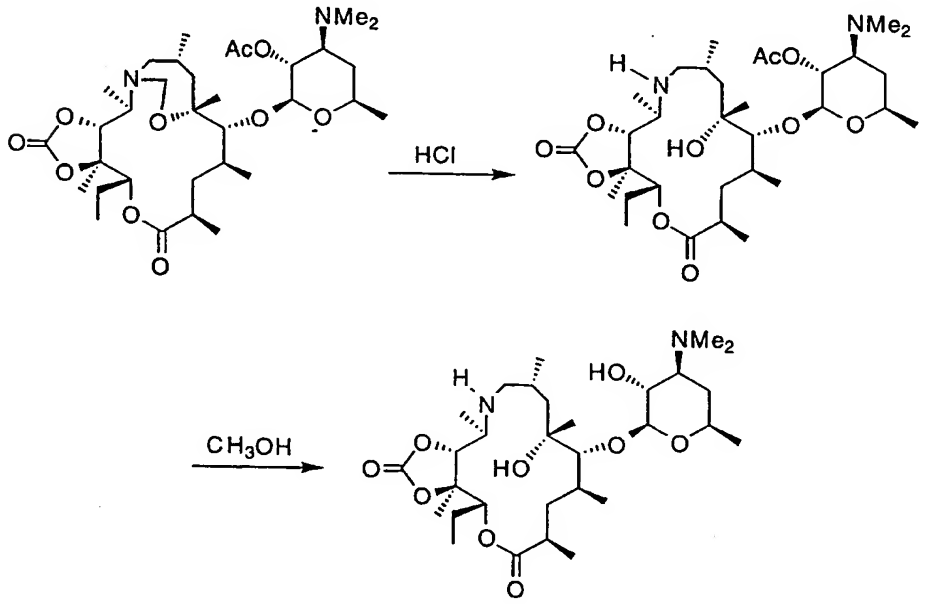


Step 1: 3-descladinosyl-3-O-methylxanthyl-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-3-O-methylxanthyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (11 mg) in methanol (4 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure and the residue lyophilized from benzene to afford the title compound.

EXAMPLE 9

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (20.0 mg, 0.031 mmol) in 1 ml 0.25 M HCl is stirred at room temperature for 3 hours. The mixture is added to $CHCl_3$, neutralized with sat. aq. K_2CO_3 and extracted with $CHCl_3$. The combined organic

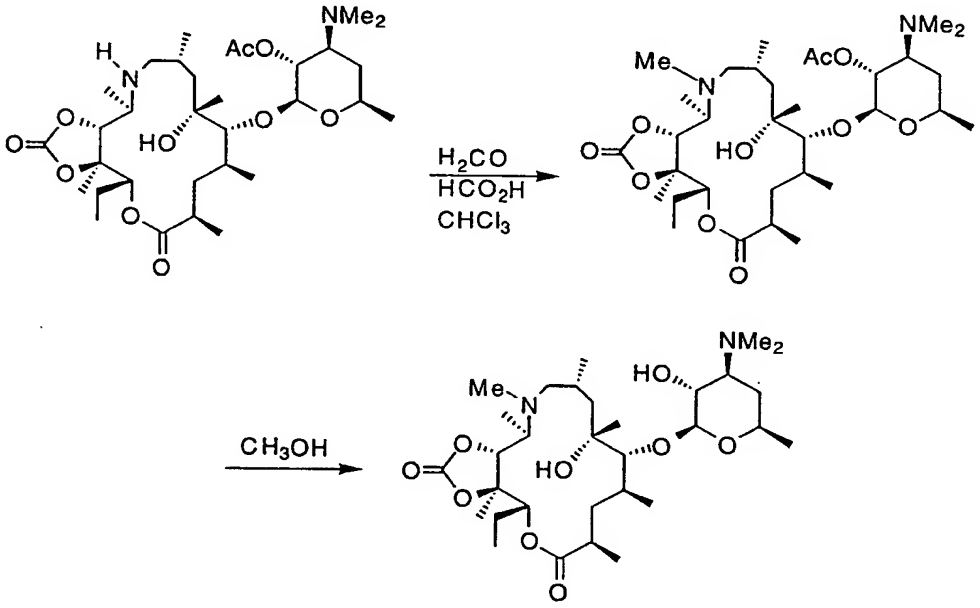
layers are washed with sat. aq. K_2CO_3, dried over anhydrous K_2CO_3, filtered, and evaporated to afford 9.6 mg of the title compound.

Step 2: 3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (9.4 mg) in methanol (2 mL) is stirred at room temperature overnight. The solvent is removed under reduced pressure and the crude product is purified by chromatography on a silica gel column eluted with 1:1 (90:10:1 CH_2Cl_2:CH_3OH:methanolic NH_3):CH_2Cl_2 to produce the title compound.

EXAMPLE 10

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A 11,12-carbonate



Step 1: 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-methyl9a-homoerythromycin A 11,12-carbonate

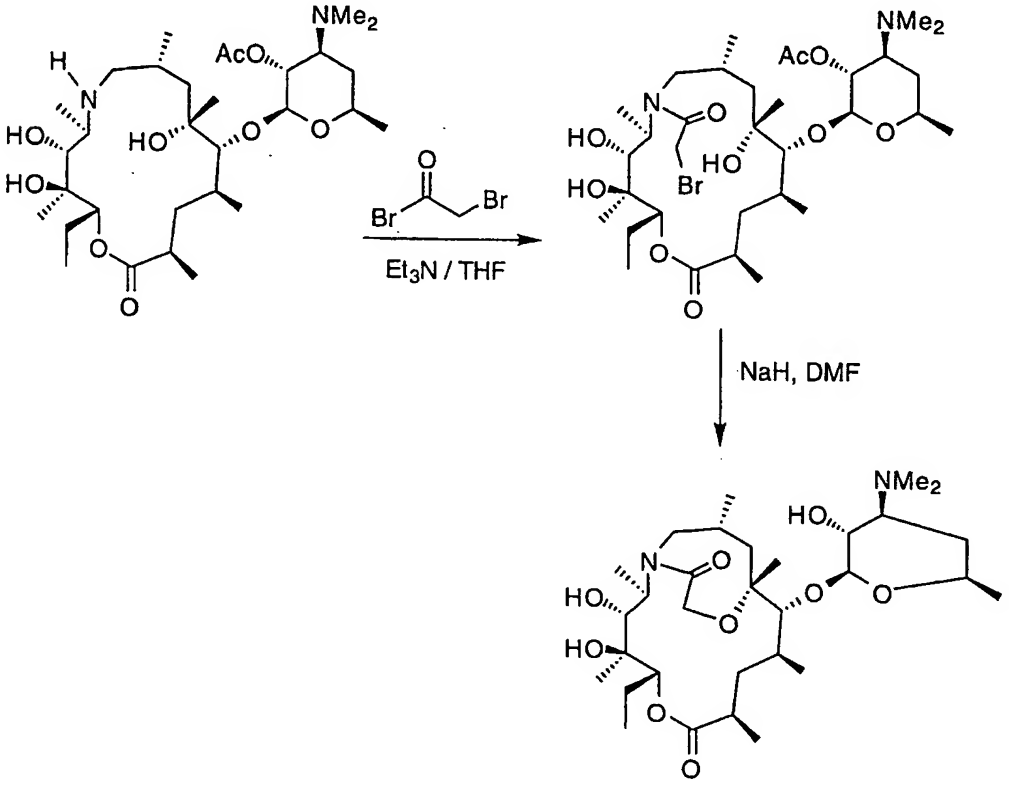
Formaldehyde (0.0080 mL, 0.109 mmol) and formic acid (0.0090 mL, 0.212 mmol) are added to a solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (64 mg, 0.101 mmol) in chloroform (1 mL). The reaction mixture is stirred at 60°C, then diluted with dichloromethane and water. The pH is adjusted to ~ 4-5 with glacial acetic acid. The organic layer is separated and the aqueous layer extracted with dichloromethane. The organic layer is washed, dried over anhydrous K_2CO_3, filtered, and evaporated to afford the title compound.

Step 2: 3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A 11,12-carbonate

A solution of 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A 11,12-carbonate (62 mg, 0.096 mmol) in methanol (5 mL) is stirred at room temperature. The solvent is removed under reduced pressure and the crude product is purified by chromatography on a silica gel column eluted with 1:1 hexane:acetone.

EXAMPLE 11

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-N,6-O-(1-oxoethylene)-9a-homoerythromycin A



Step 1: 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-N-bromoacetyl-9a-homoerythromycin A-11,12-carbonate

To 50 mg (0.080 mmol) of 2'-O-acetyl-3-descladinosyl-3-deoxy-9-deoxo-8a-aza-8a-homoerythromycin A-11,12-carbonate in 1.5 mL of freshly distilled THF (under N_2 atmosphere) is added 0.022 mL of triethylamine (0.160 mmol). After stirring the reaction mixture for 2 minutes, 0.028 mL of bromoacetyl bromide is added to the reaction, and the reaction is stirred to completion, as monitored by TLC. The reaction mixture is extracted with ethyl acetate. The organic layer is washed three times with saturated aqueous $NaHCO_3$, dried over anhydrous K_2CO_3, filtered, and the solvent is removed under reduced

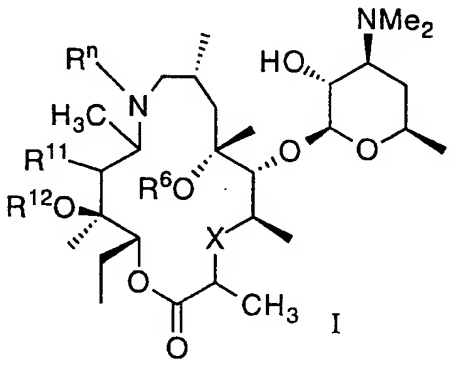
pressure. The crude product is used in the next step without furthur purification.

Step 2: 3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-N,6-O-(1-oxoethylene)-9a-homoerythromycin A

The product of the previous step is dissolved in 2.5 mL of anhydrous DMF and NaH 26 mg is added . The reaction mixture is stirred at room temperature for 2.5 hours under a N_2 atmosphere, and extracted into ethyl acetate. The organic layer is washed with saturated aqueous $NaHCO_3$ and the aqueous wash is back extracted with EtOAc. The combined organic layers are washed with $NaHCO_3$, dried over K_2CO_3, filtered, and the solvent is removed under reduced pressure. The crude product is purified by silica chromatography eluted with 1:1 hexane:acetone. The fractions containing the desired material are combined and solvent removed under reduced pressure to provide the title compound.

WHAT IS CLAIMED IS:

1. A compound represented by formula I:

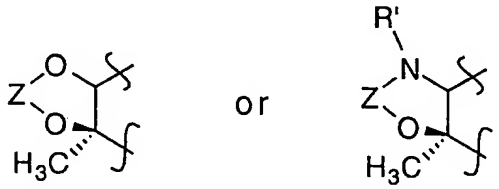


I

or a salt or hydrate thereof wherein:

R^{11} and R^{12} are taken separately or together;

when taken together, R^{11} and R^{12} taken with the intervening atoms form an additional ring as shown in the following structure:



wherein R' and Z are as defined below;

when taken separately, R^{11} is selected from the group consisting of: OH, OCH_3, NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$, and

R^{12} represents a member selected from the group consisting of: H, C1-6 alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined below,

$(CH_2)_n$ is alkylene, wherein n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2,

NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

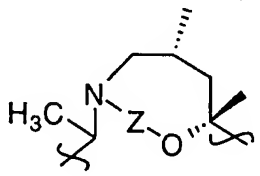
X represents CH_2 , CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S or CHOR;

R represents H, CS_2CH_3, phenyl or C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

R^n represents H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above, and

R^6 represents H or CH_3,

or R^6 and R^n are taken in conjunction with the intervening atoms and form an additional ring as shown in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", $P(O)NR^nR"$, $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 in which X is as defined above;

R^z represents C_{1-6} alkyl or phenyl;

R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined, and

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as previously defined.

2. A compound in accordance with claim 1 wherein X contained in the azalide ring represents CH_2, CHF or CF_2.

3. A compound in accordance with claim 1 wherein X represents $C=CH_2$, C=S or CHSR.

4. A compound in accordance with claim 1 wherein X represents $CHCH_3$ or CHOR.

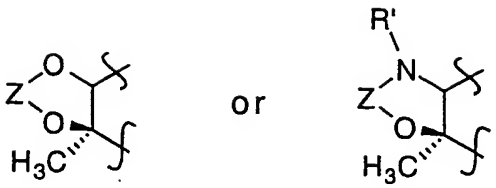
5. A compound in accordance with claim 1 wherein R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$, and R^6 is H or CH_3.

6. A compound in accordance with claim 1 wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl.

7. A compound in accordance with claim 1 wherein R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined.

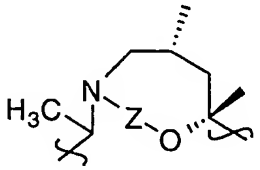
8. A compound in accordance with claim 1 wherein R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$.

9. A compound in accordance with claim 1 wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring of the following structure:



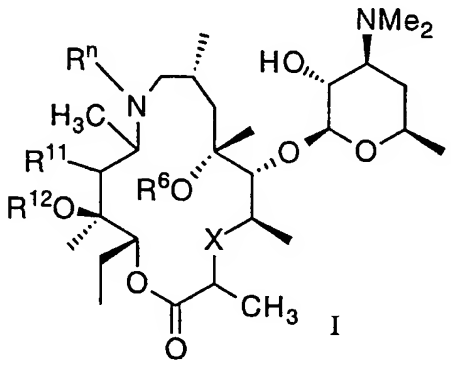
wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

10. A compound in accordance with claim 1 wherein R^6 and R^n are taken together with the intervening atoms form a ring as shown in the following structure:



in which Z is as originally described.

11. A compound represented by formula I:

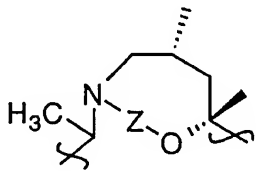


I

or a salt or hydrate thereof, wherein:
X represents CH_2, CHF or CF_2;
R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:

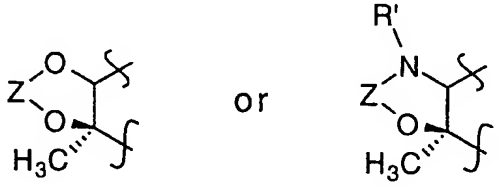


Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

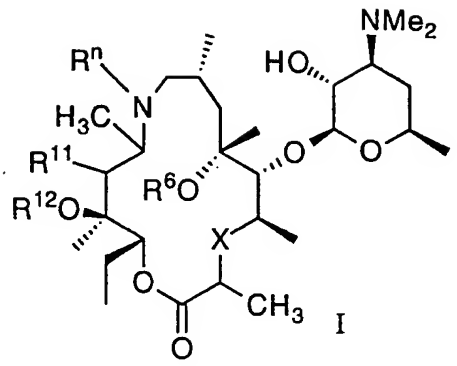
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

12. A compound represented by formula I:



I

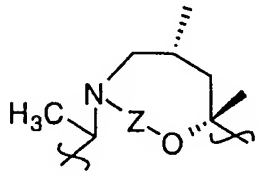
or a salt or hydrate thereof, wherein:

X represents $C=CH_2$, C=S or CHSR;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:

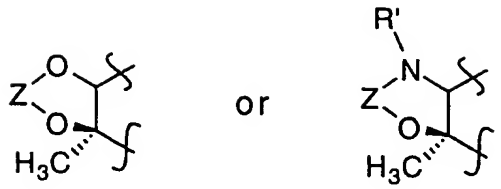


Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

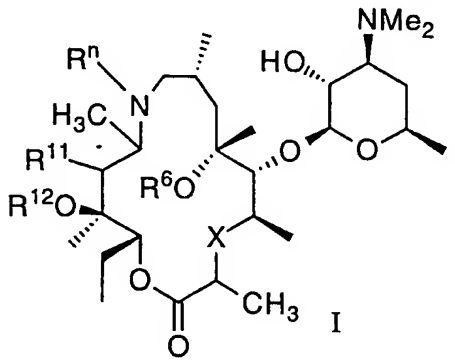
R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

13. A compound represented by formula I:



I

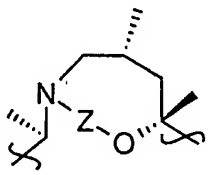
or a salt or hydrate thereof, wherein:

X represents $CHCH_3$ or CHOR;

R^n represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

R^6 is H or CH_3;

or R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:



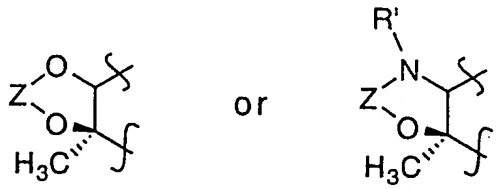
Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S

and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} is selected from the group consisting of OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as originally defined;

R^{12} represents H, C_{1-6} alkyl or $(CH_2)_nAr$;

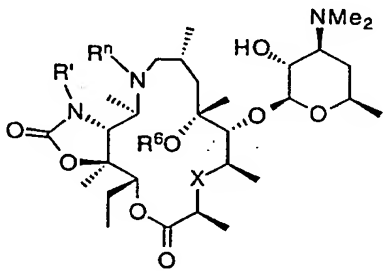
or R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring disclosed in the following structure:

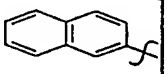
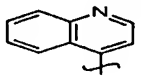
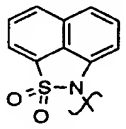
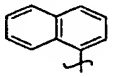
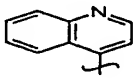
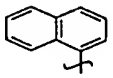


Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

14. A compound in accordance with claim 1 falling within one of the following tables:

Table 1



#	X	R^n	R^6	R'	Ar
1	CH_2	CH_3	H	$(CH_2)_4Ar$	
2	CH_2	CH_3	H	$(CH_2)_4Ar$	
3	CH_2	CH_3	H	$(CH_2)_4Ar$	
4	CH_2	CH_3	H	$(CH_2)_3Ar$	
5	CHF	CH_3	CH_3	$(CH_2)_4Ar$	
6	CF_2	CH_3	CH_3	$(CH_2)_4Ar$	
7	CH_2	---CH_2---		$(CH_2)_4Ar$	

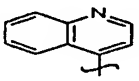
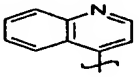
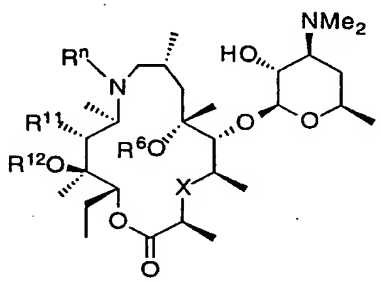
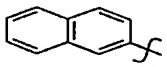
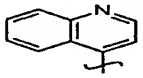
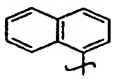
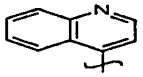
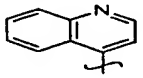
8	CH_2	---CH_2---		$NH(CH_2)_3Ar$	
9	CH_2	CH_3	H	$NH(CH_2)_3Ar$	

Table 2



#	X	R^n	R^6	R^{11}	R^{12}	Ar
10	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
11	CH_2	CH_3	H	OH	$(CH_2)_3Ar$	
12	CH_2	CH_3	H	$O(CH_2)_3Ar$	H	
13	CHF	CH_3	CH_3	$O(CH_2)_4Ar$	H	
14	CH_2	CH_3	H	$S(CH_2)_4Ar$	H	
15	CH_2	$(CH_2)_4Ar$	H	OH	H	

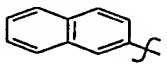
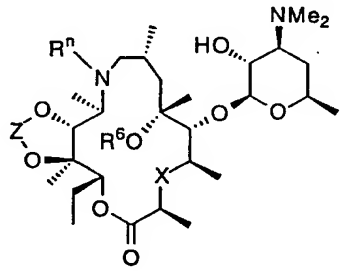
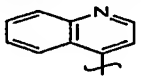
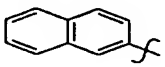
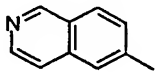
16	CH_2	$(CH_2)_4SO_2Ar$	H	OH	H	
17	C=S	CH_3	CH_3	OH	H	------
18	CH_2	$-P(O)OCH_3-$		OH	H	------
19	C=S	$-P(O)OCH_3-$		OH	H	------
20	CH_2	$-COCH_2-$		OH	H	------
21	C=S	$-COCH_2-$		OH	H	------

Table 3



#	Z	X	Rn	R6	Ar
22	$C=N(CH_2)_3Ar$	CH_2	CH_3	H	
23	$P(O)O(CH_2)_3Ar$	CH_2	CH_3	H	

24	P(O)NH(CH2)3Ar	CH2	CH3	H	

15. A compound in accordance with claim 1 having the name:

9-Deoxo-9a-aza-9a-methyl-3-descladinosyl-9a-homoerythromycin A-11,12-carbonate;

3-O-Acetyl-9-deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate;

9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxyethoxymethyl-9a-homoerythromycin A 11,12-carbonate;

9-Deoxo-9a-aza-9a,6-O-methylene-3-descladinosyl-3-O-methoxymethyl-9a-homoerythromycin A-11,12-carbonate;

9-Deoxo-9a-aza-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate;

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A-11,12-carbonate-9a-N,-6-O-carbamate;

3-descladinosyl-3-deoxy-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate;

3-descladinosyl-3-O-methylxanthyl-9a-N,-6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate;

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate, or

3-descladinosyl-3-deoxy-9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A 11,12-carbonate.

16. A pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

17. A method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12174

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/33, 31/70; C07D 267/00; C07H 5/04, 5/06, 17/08
US CL :514/183; 536/7.1, 7.2, 7.3, 7.4, 18.7; 540/467, 468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183; 536/7.1, 7.2, 7.3, 7.4, 18.7; 540/467, 468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 691 464 A1 (ROUSSEL-UCLAF) 26 November 1993, page 7, lines 3-6.	1, 4-8, 13, 16 and 17
X	EP 0 283 055 A2 (SOUR PLIVA FARMACEUTSKA) 21 September 1988, page 7, example 3 and page 10, example 15.	1, 4-8, 13, 16 and 17
X	DJOKIC et al., Erythromycin Series. Part 13. Synthesis and Structure Elucidation of 10-Dihydro-10-deoxo-11-methyl-11-azaerythromycin A. Journal of Chemical Research. May 1988, No. 5, pages 152-153, especially page 152, compounds 17 and 19.	1, 4-8, 13, 16 and 17

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 24 SEPTEMBER 1998	Date of mailing of the international search report 29 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MUKUND SHAH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12174

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DJOKIC et al., Erythromycin Series. Part 11. Ring Expansion of Erythromycin A Oxime by the Beckmann Rearrangement. Journal of the Chemical Society, Perkin Trans I. 1986, No. 11, pages 1881-1890, especially page 1887, compound 12.	1, 4-8, 13, 16 and 17